Division of Research Services

Fiscal Year 1989 Annual Report

Proud to Serve 1956-1990

Division of Research Services

FY 1989 Annual Report

Dr. Robert A. Whitney, Jr., Director, DRS, with personnel of the DRS Office of the Director and the NIH Office of Animal Care and Use. (Photograph taken for the first DRS Employee Recognition Day, June 1, 1989.)

A Letter From the Director

Robert A. Whitney, Jr., D.V.M.
Director
Division of Research Services
National Institutes of Health

As this annual report was about to be set in type for printing, we received word that Dr. Louis W. Sullivan, Secretary of Health and Human Services, has approved the merger of the Division of Research Services and the Division of Research Resources as the National Center for Research Resources (NCRR). The administrative staff of DRS and DRR have prepared well for this merger since Dr. James B. Wyngaarden, then Director, NIH, proposed it in October 1988. The four branches of DRS are about to become the intramural programs of the NCRR, while the six DRR programs will become NCRR's extramural programs. Recruitment will begin immediately for the positions of Deputy Director for Intramural Research Resources and Deputy Director for Extramural Research Resources.

DRR and DRS were long considered possible candidates for merger because of their similar missions and the benefits obtainable from greater information exchange between their programs on research resource issues, particularly biomedical engineering, instrumentation, and animal and nonanimal modeling. Our lengthy period of preparation has given us every reason to believe that the National Center for Research Resources not only will continue these two Divisions' traditions of excellence, but will integrate and extend them. Our prime research resources are our own people.

This final annual report of DRS activities before the merger illustrates the dedicated service to the NIH intramural research that will continue in the NCRR intramural research resources programs.

A productivity study now being conducted in MAPB completes a series of such studies of all four DRS branches and the Office of the Director. The series started in the Veterinary Resources Branch in 1984. These studies, conducted under contract using evaluation set-aside funds, have delivered the most comprehensive evaluation of DRS ever undertaken. Throughout, primary consideration was given to the needs of NIH intramural investigators and to their ratings of DRS services. By implementing recommendations in these studies as well as other initiatives of the branches, we have made many improvements in our services to the NIH intramural research community and in our collaborations with its members.

The first study, in VRB, led to the Branch's new emphasis on providing holding of animals during research, plus the technical services that investigators need in using these animals. Large-scale production of rodents and breeding of dogs—services now available from outside sources—were discontinued to provide NIH intramural investigators with badly needed facilities and personnel for animal research project support.

In the few years since VRB implemented these improvements, tremendous change and development have been seen in animal care and use activities at NIH. A complex initiative to make the entire NIH intramural animal care and use program accreditable by the American Association for Accreditation of Laboratory Animal Care (AAALAC) will be completed in December 1990. VRB (which has been AAALAC-accredited since 1966) plays a number of important roles in this initiative. VRB has conducted a separate management study during FY 89 to keep pace with the rapid change and development at NIH and to increase the Branch's responsiveness to the intramural research programs' current and foreseeable needs; the VRB portion of this report discusses this study.

Division of Research Services
FY-89 Budget
(In thousands of dollars)

Branch	Management	Service & Supply	Total
Veterinary Resources	$ 7,402	$12,649	$20,051
Biomedical Engineering & Instrumentation	3,867	9,097	12,964
Library	5,567	—	5,567
Medical Arts & Photography	—	7,685	7,685
Sub Total	$16,836	$29,431	$46,267
*Office of Animal Care and Use	914	—	914
Total	$17,750	$29,431	$47,181

*Organizationally assigned to OD/NIH, Administratively supported by DRS

The reports of the Branches reflect many of the continuing improvements to their programs stemming from recommendations in these studies and from spontaneous initiatives of management and staff. The Biomedical Engineering and Instrumentation Branch's recent initiatives in selling new equipment to NIH laboratories through DELPRO and in offering laboratory-wide, full-service instrument maintenance contracts can save both time and money for research programs. The NIH Library's provision of access to its automated catalog/circulation system through investigators' lab or office computers is typical of the library's alertness to the service potential of automation. The Medical Arts and Photography Branch has moved quickly to incorporate computerized graphic art design and computerized generation of scientific data slides into its repertoire of services. The Veterinary Resources Branch, which has always provided consultation and diagnostic services on request to NIH investigators and veterinarians, is now at work on establishment of a comprehensive animal health surveillance and diagnostic service as part of NIH's unified animal research program.
The Office of the Director, DRS, has also benefitted from productivity study initiatives to make our long-term planning more effective. One aspect of our implementation of these studies is a revised brief mission statement. It may undergo refinements, but I am happy to quote it here as an expression of our role within NIH.

"DRS plans and conducts a centralized program contributing to the advancement of NIH research by providing resources for the tasks of planning, executing, analyzing and reporting the findings of research projects as follows:

(a) provides applications of engineering, mathematics, physics, and the physical sciences to the solution of problems in biology and medicine, and provides technical support services related to the fabrication of new devices, the repair, maintenance, and calibration of scientific apparatus, consultation on choice of equipment, and the rental of such equipment;

(b) provides professional and technical support services related to the care and use of animals, including the provision and care of research animals, research consultation, and disease prevention/diagnosis/control services;

(c) provides comprehensive research library support to NIH scientific, clinical, and management programs through an extensive collection of books and journals, access to computer information banks, translation, and staff assistance and consultation in information handling and retrieval;

(d) provides a complete visual communications program utilizing design, graphics, medical illustration, photography, and video recording for documentation of medical research programs and data for all NIH information dissemination needs; and

(e) provides administrative support for the Office of Animal Care and Use, OD/NIH."

And second, a new statement of objectives:

"Regardless of support type, four basic Division objectives are:

- **Provide support/contribution that investigators need,**
- **Provide support in accessible, responsive manner,**
- **Assure an optimal level of quality,**
- **Contain cost."**

On June 1, 1989, DRS celebrated its first Employee Recognition Day, recognizing a wide variety of contributions by individual employees and groups to DRS and NIH activities. It was also an opportunity for getting better acquainted and enjoying some good music and food together! The group photographs appearing in this year's report were taken for that event, and show all the employees who were able to be present one morning in May. I am glad of the chance to use the pictures again, as a token of our gratitude for the excellent services provided by the dedicated employees of the Division of Research Services.

The Division of Research Services

The many specialized functions of the Division are designed to support all of the 21 Institutes, Centers, and Divisions (ICDs) that constitute the National Institutes of Health. The primary program emphasis, however, is directed at serving the intramural program, including approximately 4,800 doctoral level staff scientists and fellows who conduct research in NIH laboratories.

Organizationally, the Division is structured to provide products and services in support of the sequential steps in every biomedical research project: planning, making available models and substrates, manipulating and measuring research materials, and recording and communicating research results. Many research projects require the services of all four branches.

- The Library Branch (NIH Library) possesses or has access to virtually all published biomedical information, and its automated systems deliver the information rapidly.
- The Biomedical Engineering and Instrumentation Branch (BEIB) uses engineering, mathematics, physics, and the physical sciences to help NIH investigators solve problems in biology and medicine, especially in measurement, modeling, and design of specialized instrumentation. BEIB also meets a wide range of instrumentation needs including fabrication, modification, maintenance, and repair.
- The Veterinary Resources Branch (VRB) supplies many professional and technical services for the care and use of research animals. Among these are breeding or purchasing needed animals, caring for them skillfully and humanely, and advising researchers on animal health, nutrition, behavior, genetics, reproduction, and care.
- The Medical Arts and Photography Branch (MAPB) meets researchers' visual communication needs by designing and making graphics and medical illustrations, photomicrography and photomacrography, and producing videocassettes of biomedical procedures.

Personnel of the Biomedical Engineering and Instrumentation Branch, DRS. (Photograph taken for the first DRS Employee Recognition Day, June 1, 1989.)

Biomedical Engineering and Instrumentation Branch

Murray Eden, Ph.D., Chief

Hyperthermia Utilizing Magnetic Resonance Temperature Imaging

The modern era of hyperthermia, artificially-induced heating of all or part of the body as a treatment for cancer, is considered to have begun in 1866. In that year the German physician W. Busch reported spontaneous regression of multiple sarcomas on the face of a 43-year-old female patient, shortly after she suffered a streptococcal skin infection accompanied by high fever. In America William B. Coley, drawing upon these observations, used injections of virulent streptococci—"fever therapy"—to treat cancer.

Although Coley had some notable successes, physicians of the time tended to regard hyperthermia as primarily a treatment for certain infections and degenerative disorders—not cancer. Two factors, however, have recently caused renewed interest in hyperthermia for cancer treatment: (1) the recognition that surgery, ionizing radiation, and chemotherapy are inadequate treatments for some cancers, and (2) the development of advanced technologies for application of hyperthermia.

In the last decade data from both *in vitro* and *in vivo* studies have shown that even though hypoxic cells and cells in S-phase (the non-multiplying stage of their reproductive cycle) are largely resistant to ionizing radiation, they remain relatively sensitive to temperatures in the range of 42 to 45 degrees Celsius (108 to 113 degrees Fahrenheit). On the basis of such studies, the Food and Drug Administration (FDA) has granted pre-market approvals (PMAs) to several companies that have developed hyperthermia systems for treatment of superficial malignant tumors.

Unfortunately, results for deep-seated tumors are not as good as for superficial tumors; it is more difficult to heat deep tumors while minimizing systemic thermal stress. Additionally, only a limited number of invasive temperature measurements are possible within the heated region, a circumstance that hampers the ability to assure that the heating is both safe and effective. For these reasons in 1983 Dr. Eli Glatstein, Chief of the Radiation Oncology Branch (ROB), Clinical Oncology Program, National Cancer Institute (NCI), asked Dr. Ronald L. Levin of BEIB's Mechanical Engineering Section to develop a hyperthermia system with completely characterized physics, that ROB could use in a series of human trials.

One of ROB's physicians was interested in applying hyperthermia to treatment of cervical cancer, so Dr. Levin and a team he assembled proceeded to characterize the electromagnetic and thermal characteristics of an apparatus intended for this type of treatment, known as the Modified Fletcher Suit. This hyperthermia applicator, built by RCA, was designed to heat a cervix using microwave energy at the same time that radioactive seeds are implanted at, or very near, the site of the tumor. The BEIB team, which now included Dr. Mark Hagmann, an expert in electromagnetics, soon determined that this applicator would be inadequate. Rather than try to develop an improved hyperthermia applicator for the cervix, Dr. Levin and the group shifted their attention to the limb-sparing protocol ongoing within the Clinical Oncology Program. This protocol is studying the relative merits of amputation versus wide local excision (with and without radiotherapy and chemotherapy) for the treatment of soft tissue sarcomas. They felt that this protocol presented an ideal vehicle for studying the physics of hyperthermia, since a leg is easily accessible and, compared to some other regions of the body, easy to model.

The group began theoretical and experimental investigations of the "mini-annular phased array (MAPA)" applicator designed by the BSD Medical Corporation of Salt Lake City, Utah. The group developed a three-dimensional whole-body heterogeneous block model of a man and a number of two- and three-dimensional models of a human extremity for theoretical studies of this applicator. The team also did experiments using various physical models of legs, as well as perfused and unperfused human lower limbs (which had been amputated for medical reasons), using nonperturbing electric-field and thermal probes.

By this time the group had been joined by Visiting Fellow Dr. Jean-Luc Guerquin-Kern, from the hyperthermia group in Strasburg, France, and Dr. Caleb Charny, from the Department of Biomedical Engineering of the Johns Hopkins University School of Medicine. After Dr. Guerquin-Kern's return to France, Dr. Hélène Coldefy joined the group from the Ecole Superieure d'Electricite, Paris, France.

The group's theoretical and experimental work resulted in the complete electromagnetic characterization of the MAPA and a reasonably good characterization of the MAPA's thermal dose. In particular, the team could now: (1) minimize the amount of energy deposited o[illegible]e

of the treated region; (2) focus radiated energy into subregions (e.g., to maximize the energy deposited in highly perfused tumors and minimize its deposition in more poorly perfused bone); and (3) estimate the minimum amount of electromagnetic energy needed to bring the tumor's temperature to the therapeutic levels of 43 to 45 degrees Celsius, all the while minimizing thermal stress to the patient's cardiovascular system.

A question remained, however: how to monitor temperature continuously in the treated region with a spatial resolution of at least one centimeter and sensitivity of one-degree Celsius? Established methods of using invasive probes couldn't achieve this goal. The group proposed to solve the problem using a magnetic resonance imaging (MRI) technique, called intra-voxel incoherent motion (IVIM), recently developed by Dr. Denis LeBihan, a Visiting Associate in the Diagnostic Radiology Department of the Clinical Center.

Others had proposed noninvasive temperature monitoring by MRI, using the temperature dependence of the parameter "T_1". Precise T_1 measurements are limited to a resolution of only 2°C/cm^2, however. The group proposed, instead, to measure the molecular diffusion coefficient, D, whose temperature dependence is larger than that of T_1.

Mapping of temperature changes could be achieved from two IVIM images, one obtained before and one obtained during heating. Together with Dr. José Delannoy, a new Visiting Fellow from the Hyperthermia Center in Lille, France, the group obtained diffusion images—and the corresponding temperature images—using a 0.5 T whole-body MRI system (Thomson CGR) in conjunction with homogeneous phantoms. The sensitivity of this method allowed temperature images to be resolved to better than 0.5°C (at least 2 times better than by using T_1 methods). Recently, a US patent was awarded to Drs. LeBihan, Delannoy, and Levin for this discovery.

To take better advantage of this new MRI technique in hyperthermia treatments, the group collaborated with Drs. David Hoult, Robert Turner, and Ching-Nien Chen, also of BEIB, to design two new MAPAs. These have the same heating characteristics as the old unit, but are electromagnetically compatible with either the Thomson-CGR 0.5 T or the GE Signa 1.5 T whole-body magnetic resonance imaging (MRI) systems. In tests of the compatibility of these new MAPAs with the MRI units, the group alternated heating of a doped acrylamide gel phantom with recording of data for imaging (typically 700 msec of heating, followed by 300 msec of imaging). Using measurements from fiber-optic probes inserted into the gels as a reference, the noninvasive IVIM technique produced highly accurate temperature images. The temperature resolution was better than 0.5°C temperature, the spatial resolution was better than one centimeter, and the measurements took only one minute on the Signa MRI system. Drs. Delannoy, LeBihan, Turner, Chen, and Levin have applied for a Federal patent on the combined MRI-hyperthermia probe assembly.

In short BEIB developed a hyperthermia system able to deliver heat accurately, effectively, and with precise control to deep-seated tumors—fulfilling our original charge from Dr. Glatstein of ROB. A Phase One clinical protocol, permitting the system to be tested on patients, has recently been approved.

BEIB in FY 1989

BEIB has been busy fulfilling its commitment to provide the NIH research community with a broad range of scientific and engineering expertise. BEIB's staff of approximately 40 physical scientists and engineers and 75 technical support personnel have collaborated in more than 200 projects to produce advanced instrumentation, models, methods, and techniques dedicated to the acquisition of biomedical information previously unavailable to NIH's scientists. In addition, they have responded to 1,400 requests for fabrication or major modification of laboratory devices and nearly ten thousand requests for repairs and minor modifications to scientific equipment.

Status of Current Activities

Over the years, BEIB has initiated several projects that are interdisciplinary in character and do not fit readily within the sectional structure of BEIB. At present there are four such areas being carried out directly under the administrative control of the Office of the Chief. They are: nuclear magnetic resonance instrumentation, electron beam imaging and microspectroscopy, analytical ultracentrifugation, and image processing. In what follows we will give a brief overview of the activities of these groups, followed by the activities of BEIB's engineering sections, and Scientific Equipment Services.

Nuclear Magnetic Resonance Instrumentation

BEIB continues to explore and support the numerous research opportunities presented by the in vivo application of nuclear magnetic resonance. Work has focused on three main areas: the design and construction of specialized radio frequency coils, the development of new spin "massaging" techniques, and the implementation of echo-planar imaging, a method intended to produce images in under 100 milliseconds.

New spin techniques have been implemented. These include: selective noise pulses that effectively "scramble" magnetization over a well-defined region and thereby suppress unwanted signal; modification of the well-known STEAM and PRESS sequences to obtain proton spectra from 0.5 ml volumes in the heads of cats; new echo-planar imaging sequences that monitor diffusion and use asymmetric gradient switching to obtain resolutions of under 0.5mm.

A large construction project has resulted in the fabrication of a shielded-gradient coil system for NIH's two-tesla magnet, and the coils are now ready for testing. At the same time, powerful local z-gradient coils, for use with echo-planar and diffusion measurements, have been built and successfully tested. Coils have also been made for localized spectroscopy on animals and for echo-planar head imaging at 64 MHz.

As mentioned at the beginning of this report, NMR may be used to monitor temperature noninvasively (via measurement of water's diffusion constant). We have expended considerable effort to develop dual-purpose probes that 1) give the NMR signal and 2) create an intense radio-frequency electric field for localized hyperthermia in cancer patients.

Finally, the writing of a book, *Biomedical Magnetic Resonance Technology*, has been completed, with publication expected early in FY90; a sensitive way of monitoring residual B_o gradients following gradient switching has been invented; a novel energy transfer system for rapid gradient switching has been devised (patent applied for), and the In Vivo NMR Research Center's computing system has been refined and improved.

Electron Beam Imaging and Microspectroscopy

BEIB has continued development of its high resolution scanning transmission electron microscope (STEM) capability and applying it to new classes of biological studies. We tested a new cryotransfer sample stage and found it to be mechanically and thermally stable at temperatures of -175°C. Preliminary image data from hydrated ice-embedded microtubule and virus preparations have been obtained in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Digitized elastic dark-field STEM images were acquired at low dose with single electron sensitivity, using a PC computer interfaced to the field emission STEM. Test data show that this system can be used to determine masses of protein macromolecules using known molecular weight structures as references.

A modified parallel detection electron energy loss spectrometer (EELS) has been installed on the field emission STEM and the energy resolution has been demonstrated to be 0.35 eV, which is better than has been obtained in any other laboratory. Studies are being performed to compare sensitivity for elemental analysis using EELS with that obtained using an ultra-thin-window energy-dispersive x-ray detector. Considerable progress has also been made with the development of new spectral and imaging software for X-ray microanalysis, based on a Macintosh II computer. In collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) measurements have been made to determine the composition of individual secretory granules in pancreatic islet of Langerhans cells prepared by cryoultramicrotomy. Granules in beta cells contained high level of sulfur and zinc, attributed to insulin storage organelles. Although most granules in the glucagon-secreting alpha cells contained no detectable zinc, some beta-like granules, surprisingly, were found in these cells too. In other work we are making progress toward labeling of brain tissue with a variety of pharmacological probes, including fluorine-labeled tracers.

Analytical Ultracentrifugation

Research in the area of physical chemistry of biological macromolecules has involved collaborations with several Institutes within NIH. Extensive effort has been given to using personal computers for high-speed data acquisition and analysis. Additionally, in a collaboration with NIDDK, we have developed new methods for rapidly obtaining sedimentation coefficients, diffusion coefficients, and molecular weights. In other collaborations with NIDDK, we have initiated studies on the thermodynamics of reversible monomer-dimer association of small oligonucleotides, in order to elucidate the relationship between structure and the values of characterizing thermodynamic parameters. Studies on the polymerization of actin and on actin-actobindin interaction have been carried out in collaboration with the National Heart, Lung, and Blood Institute (NHLBI).

Studies of the interactions of fibrinogen with various plasma proteins involved in the clotting and fibrinolytic process have continued in a collaboration with the National Institute of Dental Research (NIDR). Studies on the associative properties of synapsin have continued with NCI. Further progress has been made in the techniques of mathematical modeling used for the analysis of data obtained in these studies and has significantly enhanced the quality of the results obtained.

Image Processing
High-resolution micrographs are often of poor quality, due to a variety of distortions and a very low signal-to-noise ratio. For micrographs of multiple or repetitive structures—such as an image of many virus particles—visual quality can be improved significantly by using correlation-averaging techniques. This, however, requires methods to compensate for the slight variations in the geometry and orientation of the objects to be averaged. We have designed an iterative procedure that compensates for spatial deformation in quasi-periodic structures and allows noise reduction by averaging. We have, for example, applied this technique to the analysis of skeletal muscle filaments.

Echocardiography is a noninvasive method for monitoring ventricular function and evaluating myocardial hypertrophy. Although the information displayed in two-dimensional echocardiograms is generally the most useful for diagnostic purposes, one-dimensional or M-Mode echocardiography, is widely accepted as the reference method for the evaluation of myocardial wall thickness, due to its greater reliability. We have developed two algorithms, intended to run on a Macintosh II workstation, for processing M-mode echocardiograms: the first allows automated extraction of myocardial borders, and the second compensates in a fully automated way for variations in heart rate.

Textural information can play an important role in interpretation of biomedical images, such as X-rays and ultrasonic recordings. We have developed a means to partition an image into regions of similar texture using textural features extracted by linear filtering. An important component of this system is a new multi-resolution feature-reduction module that offers substantial performance improvement over conventional approaches, such as principal component analysis or Karhunen-Loève transform.

It is desirable to reduce the measurement noise present in biomedical images, such as high-resolution micrographs, echocardiograms, or PET scans. Conventional linear filtering techniques perform well for homogeneous regions but tend to degrade sharp image transitions. In order to preserve the edge information, we have designed an adaptive least squares post-filtering procedure that computes localized, linear combinations of the initial noisy image and its filtered version. This method is very efficient and allows an *a posteriori* compensation of some of the deficiencies of conventional noise reduction techniques.

Until very recently, the integration of image processing systems required considerable expense for specialized hardware, in addition to a major programming effort. As a consequence, image processing has been accessible only to a minority of privileged researchers. Hardware is now more affordable, with the advent of powerful microcomputers, but their programming using conventional techniques is notoriously difficult, due to the high level of sophistication of their user interface. We have developed several software tools that facilitate the development of specialized image processing software on Macintosh II workstations. The first is a user interface that is extremely easy to modify for creating specialized applications; its main feature is that complex interactions are handled automatically—the programmer need only be concerned with application-specific procedures. The second is a comprehensive set of basic image-processing modules. At present, our software library includes about 200 FORTRAN subroutines that perform image processing tasks, such as filtering, edge detection, point transformations, and binary operations.

Previous methods to interpret zonal or polydisperse gel patterns of two-dimensional Serwer-type gels for the size and free mobility (surface net charge density) of each component could not simultaneously measure the abundance of the components. Our work advances the method by specifying the relative concentration of each component on the basis of densitometric analysis of the pattern. We have implemented the requisite mathematical routines in a user-friendly software package for use on a personal computer.

Applied Clinical Engineering Section
The Applied Clinical Engineering Section (ACES) supports basic and clinical research in laboratories located within the NIH Clinical Center and elsewhere at NIH. The scope of its support ranges from analytical and experimental services to the design and development of biomedical instrumentation in a variety of areas, including microcalorimetry, thermal measurement, electro-optics, microelectronics, transducer design, automated data collection and analysis, blood pressure and flow measurement, and hardware and software design for microcomputer-based systems.

By way of example, last year ACES developed a unique PC-based data acquisition and analysis system for sleep disorder studies. It allows multi-channel temperature and EEG signals to be studied as indicies of sleep disorder.

Additionally, microcalorimeter developments have increased the capability of stopped-flow systems for studying complex interactions between DNA and drugs. Recent studies have produced dramatic results at previously unmeasurable heat levels (5-10 microjoules).

With the Liver Disease Section of NIDDK, ACES developed a transducer, supporting electronics, and software to monitor scratching by patients suffering from cholestatic diseases, such as biliary cirrhosis, and to gauge the effectiveness of drugs intended to relieve itching. Effective medications might forestall the need for liver transplantation, the only therapy currently available to ameliorate the chronic, sometimes unbearable itching of such diseases.

ACES continues to collaborate with the Laboratory of Chemical Biology, NIDDK, on development of noninvasive monitoring techniques for sickle cell disease. These studies include determining the accuracy of pulse oximeters for monitoring oxygen saturation in sickle cell blood and monitoring the effects of new treatments on microvascular blood flow.

The Section has developed methods for the noninvasive determination of tooth vitality, based on the optical measurement of oxygen saturation of blood in tooth pulp. We are also constructing mathematical and physical models of light scattering and absorption in tissue to elucidate the theoretical basis of pulse oximetry. Results of these studies will assist in the development of novel types of oximeters.

Reflective pulse oximeters are being developed in collaboration with the Department of Anesthesiology, Clinical Center (CC). In addition to the prototype devices being developed, theoretical and experimental studies are being conducted to determine optimum design parameters for these instruments.

In collaboration with the Laboratory of Cell Biology and Genetics of NIDDK, a system for measuring membrane capacitance of cell channels was developed on a PC-based microcomputer system using whole-cell patch-clamp technology. We will assist our collaborators in measuring the effects of various chemical proteins on such capacitance in beta and chromaffin cell.

Additionally, ACES developed several workstations intended for high-performance liquid chromatography. The workstations are interconnected using a token-ring network of PCs.

The Medical Neurology Branch of NINDS collaborated with ACES in the design of a system to obtain real-time measurements of electroencephalographic (EEG) spikes. The system is used to screen anticonvulsants.

ACES continued to participate in clinical engineering activities within the Clinical Center, including investigating all incidents in which persons are injured by electricity. We also reviewed and monitored other aspects of electrical safety and equipment standards through representation on the Clinical Center Safety and Standardization Committee.

Chemical Engineering Section

The Chemical Engineering Section provides support to the NIH in pharmacokinetics, transport phenomena, fluid mechanics, and instrumentation. Major collaborative research and development projects typically involve one or more engineering staff members and researchers from the biomedical sciences in a close interaction intended to increase understanding of biological processes and improve clinical practice.

In the past year we have employed structure-activity analysis to identify new sulfone compounds that exhibit strong activity against *Toxoplasma gondii*, a protozoan capable of inducing serious infection in AIDS patients. Since it has been observed that most of these patients can tolerate dapsone, the only commercially available sulfone active against *T. gondii*, we have sought additional (but more effective) agents amongst this class of compounds. Several sulfone analogs were identified as potent inhibitors. None of the analogs, however, was more active than dapsone itself. Accordingly we used a Fujita-Ban formalism to determine the contributions of each analog substituent to drug potency and to assess whether new combinations of these substituents could lead to improved analogs. Of 21 moieties investigated, four substitutions on dapsone were found to be most likely to potentiate activity against *T. gondii*. Testing of one of these, the 3'-Cl derivative, against intact organisms revealed a five-fold increase in activity over that obtained with dapsone.

Principles of chemical reaction engineering have been applied to the development of pharmacokinetic models for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and humans. They provide a plausible set of equations useful in extrapolation of data from experimental animals to humans, thereby improving chemotherapy and risk assessment. For example, work is in progress on the development of a pharmacokinetic model for the distribution and disposition of methyl mercury and inorganic mercury in the rat and on the adaptation of a published model for cisplatin to the analog carboplatin.

Consideration of regional drug delivery has continued with emphasis on intra-arterial and intracavitary administration. Drug streaming from arterial catheters appears to be a frequent problem leading to nonuniform distribution of drug in the infused tissue, thereby compromising studies of toxicity and therapeutic effect. Nonuniform distribution of tracers, first demonstrated in rats, monkeys, and *in-vitro* models, has been demonstrated in human subjects by means of position emission tomography

of oxygen-15-labelled water. It is particularly severe during slow, steady supraophthalmic infusions, but can be greatly reduced by means of diastolically-phased high-velocity pulsed infusions.

Studies are under way on the pharmacokinetics and tumor transport of macromolecular toxins, such as diptheria toxin (DT) and the immunotoxin 454A12-CRM107. By an *in-vitro* assay, DT and 454A12-CRM107 exhibit similar toxicities to a number of human tumor cell lines. The plasma kinetics of the toxins in nude mice showed a biphasic decay consistent with a rapid distribution phase and a slow elimination phase. We are studying the effect of the size and binding of the toxins on transport to and accumulation in a human tumor grown in the flank of the nude mouse.

Vitreous fluorophotometry is a clinical procedure for measuring the spatial distribution of fluorescence along the optical axis in a human subject's vitreous, following administration of a fluorescent dye. Such a technique may prove useful, for example, in monitoring the progression of diabetic retinopathy. We have developed an analysis scheme that largely overcomes deficiencies in existing analysis protocols.

Microdialysis probe technology provides a means for sampling diffusible extracellular constituents in tissue. However, the relationship of the probe effluent concentrations to their tissue counterparts is a complex function of solute molecular weight, solute physiochemical properties, tissue properties, probe membrane properties, probe geometry and perfusion rate, and the trauma of probe insertion into the tissue. A general mathematical framework for quantitative microdialysis analysis has been proposed. Expressions have been derived for the dialysate, membrane, and external phase resistances for steady-state operation. The resistances were evaluated for the sampling of tritiated water from rat brain, and the results were used to compare theoretical predictions with published data. Excellent agreement was obtained. The theory clarifies the discrepancy between *in-vivo* and *in-vitro* microdialysis measurements. A mathematical solution has also been obtained for transient probe-tissue behavior, and we have validated the theory by comparisons between predicted and observed acetaminophen concentrations in dialysate and in rat brain.

The Section's work in experimental fluid mechanics has emphasized physical models of vascular systems for study of a variety of hemodynamic phenomena. Such models are useful tools, because they allow the investigator to conduct experiments under controlled laboratory conditions. They can also reduce the need for animal experiments by substituting for them in some cases and suggesting economical experimental design in others. Flow in models of human coronary arteries has been studied by means of hot film and electrochemical probes. It is observed that flow in casts of normal coronary arteries shows some degree of turbulence at high flow rate, e.g., during simulation of exercise. The presence of an arterial stent does not increase the overall turbulence, except perhaps under high flow conditions in a localized region distal to the stents. Other studies include laser Doppler velocity profiles and visualization of flow around spheres in a tube and the fluid mechanics of sampling through a triple-lumen catheter in a mock circulatory loop.

Electrical and Electronic Engineering Section

The objective of the Electrical and Electronic Engineering Section is to bring the power of modern electronic technology to bear on the needs of biomedical research. Special expertise in areas such as electro-optics, microprocessors, video, and general electronic circuitry has provided support for a wide variety of intramural research projects.

The focus of our electro-optics efforts is the identification of new applications for lasers in biomedical research, diagnosis, and therapy. This has involved development and evaluation of a number of laser/fiber-optic systems for microsurgery, phototherapy, and remote sensing, as well as development of a general theory for quantification of the interaction of light with tissues. A laser-Doppler technique developed to measure a variety of microcirculatory flow parameters has become a widely used research tool, and a number of commercial instruments are based on the NIH prototype and theory.

Our program with NHLBI in laser angioplasty has broadened understanding of this therapeutic modality and led developments in the field to new directions. We have demonstrated how ablation using argon and pulsed dye lasers (facilitated by pigments such as hemoglobin) may be utilized in recanalization of stenosed arteries. Moreover, the fluorescent spectra of the targets are useful in guiding the ablation procedure. We have discovered laser-induced shock wave pacing of ventricular contraction and developed means to circumvent its potential for causing arrhythmias. Having characterized inherent limitations of the excimer and flashlamp pumped dye lasers for use in angioplasty, we have discovered and developed new pulsed IR laser sources (Er:YAG @ 2.94 micrometers and Tm:YAG at 2.01 & 1.96 micrometers wavelength) exhibiting precise ablation, due to strong hydroxyl absorption at these wavelengths. Our clinical evaluation and refinement of laser ablation by fluorescence sensing of atherosclerotic plaque in peripheral vessels has led to the initiation of clinical trials of percutaneous coronary

laser angioplasty (PCLA). The severe potential risks of such procedures and the unknown long-term efficacy are major concerns in our clinical trials. Alternative angioplasty systems utilizing the Tm:YAG laser with guidance by intravascular ultrasound are being developed and evaluated.

We have applied our experience in laser photochemistry to studying means of photochemical destruction of viral and bacterial contamination in blood and blood products. One goal of this collaboration with the Center for Biologics Evaluation and Research, FDA, is to develop a non-invasive photochemical treatment of blood stored in transfusion bags to reduce the risk of transmitting acquired immunodeficiency syndrome (AIDS) and other infectious diseases. We have evaluated single and multiple-photon excitation of DNA and proteins for the dose response of human blood cells and viruses. An efficacious range of laser light doses has been determined that destroys virus, but does no significant damage to serum and platelet concentrates. Currently we are evaluating the potential of increasing therapeutic efficiency by the introduction into the blood of selective photochemicals. The effects of light and photochemical agents, alone and in combination, on blood components and infectious agents, are critical components of this investigation.

Our collaboration with Radiation Oncology Branch and the Surgery Branch, NCI, on the development of techniques for photochemical treatment of cancer has moved rapidly into human trials. This method involves direct illumination of tumors with laser light after the patient has received a photochemical (hematoporphyrin derivative) with specific activity against malignant tissue. The local photochemical generation of singlet oxygen kills the tumor cells, providing a therapy with minimal effects on normal tissue.

New instrumentation includes a second high-power dye laser that allows treatment in substantially less time, a fluorescence detector for monitoring the concentration of photochemical in tissue, and a computer-based light monitoring system to integrate the light dose measured by photo-diodes at selected locations. This information has been used to evaluate and modify the light distribution in a Phase One clinical trial. New concepts being explored include temporary use of blood substitutes to reduce attenuation of light by hemoglobin, induced temperature gradients in tissue to compensate partially for the attenuation-versus-distance characteristic, novel schemes involving phosphorescence or chemi-luminescence to provide nearly non-invasive illumination, and new approaches to singlet oxygen dosimetry.

Other new electro-optic projects include use of light selectively to lyse liposome vesicles (permitting delivery of a bolus of drug at a specific location) and a spectrophotometer capable of making readings at 100 wavelengths simultaneously every 10 microseconds.

We are continuing, too, to support the Electronic Patient Identification and Monitoring System (EPIMS) for the 12E Nursing Unit of the National Institute on Aging (NIA). Work is in progress to move the EPIMS from 12E to a newly renovated nursing unit on 6D. Funds have been budgeted for two similar systems, for the Geriatric Psychopharmacology Unit on 6W and the renovated 5E Nursing Unit. We will develop a crystal-controlled FM transmitter for the two new installations.

The support of the NIH Biotechnology Unit (Pilot Plant) continues by providing ongoing assistance and incorporating new systems and equipment for data acquisition, process control, and data analysis for production and fermentation research. New research vessels are being acquired for support of the Protein Expression Laboratory and data acquisition and control systems, similar to the ones that have been in use for several years with the 5 and 10 liter research systems. We are upgrading existing programs to incorporate real-time calculation of growth parameters, to supply additional controls, and to record data from instruments newly added to the system.

The Section is continuing to improve and expand the computer-based eye-tracking system built for the National Institute of Mental Health (NIMH). In addition to the initial purpose of testing schizophrenics, and more recently the family members of schizophrenics, the system is being used to study the effects of AIDS on the ability to track moving targets. There are now two labs in the NIMH that are using these systems, as well as St. Elizabeths Hospital.

The magneto-encephalography program in collaboration with NINDS and the Division of Computer Research and Technology (DCRT) has focused on the so-called "inverse modelling problem," correlation of MEG and EEG data, and computerized classification of epileptic discharges. Introduction of current dipoles at various locations and orientations into a model permitted experimental assessment of the effects of return currents. The principal long-range goal continues to be the spatial localization of epileptic foci in three dimensions.

The Neuro-PET (positron emission tomographic) scanner is about to be re-activated for animal research, and we will be involved in efforts to improve its spatial resolution. We also hope to exploit new techniques for coincidence detection, attenuation correction, and scatter correction for development of true three-dimensional PET scanning.

Mechanical Engineering Section

The Mechanical Engineering Section conducted a wide diversity of collaborations with scientists involving analytical and experimental studies and the development of specialized instrumentation. A substantial effort was made in the area of hyperthermia and noninvasive temperature measurement (described in the opening segment of this report). The NIH-INSERM collaboration in models in cardiovascular dynamics, which is part of the general accord in instrumentation and bioengineering, continued development of animal and mathematical models for cardiovascular disease. In one study, *in-vivo* measurements of pressure-diameter relations of arterioles was carried out in normotensive and spontaneously hypertensive rats. The measurements are being used in conjunction with a mathematical model for contracting arterioles to assess differences in active responses to pharmacological agents. In a related study, an *in-vitro* determination of rat carotid artery compliance was automated using a computer-driven servo-controlled pump. In other studies, heart shapes are computed from a theoretical biomechanical model, and compared with images from patients with heart disease. The computed images are being used to infer noninvasively the severity of hemodynamic consequences of disease states.

The section was active in planning and participted in the NIH Conference on Modeling in Biomedical Research, sponsored jointly by the Division of Research Services (DRS), the Division of Research Resources (DRR), and the Office of Medical Applications of Research (OMAR). This conference examined the status of a spectrum of biological and mathematical models currently used to study cardiovascular dysfunction and diabetes mellitus. A panel of outside experts recommended that NIH and other agencies charged with the support of biomedical research seek new means to encourage theoretical biology and to support new collaborations and models. They also concluded that the advance of modeling and model systems enhances science; it will not substitute for animal research and testing.

A confocal microscope for reflected and fluorescent light has been developed. Video rate imaging is achieved by acousto-optically scanning a laser beam and using an image dissector tube to "scan" a confocal pinhole in synchrony with the laser spot. Real time jitter-free images of a variety of biological objects have been produced. Improvements in the scanner optics are being implemented to approach diffractional limits. A transmitted light version is being designed, and the use of rapidly sequenced multiple laser wavelengths is being studied.

Progress continues in the area of electro-mechanochemistry of polyelectrolyte hydrogels—in particular their remarkable swelling behavior. The physical and chemical properties of these gels are being exploited in the design of devices that sense touch and perform mechanical work. Physical chemistry, and statistical and continuum mechanics provide the underpinnings of mathematical models that are being developed to describe the gels' equilibrium and dynamic behavior, while experiments are being performed to determine their physical and chemical properties. A novel concept for measurement of intracranial pressure, using hydrogels, is being explored.

A system is being developed to study the *in-vitro* morphological response of sickle cell erythroctyes to changes in the partial pressure of oxygen. In this system, red blood cells are placed on a slide mounted in a flow cell. A thin oxygen permeable membrane separates the cells from a stream of gas of known partial pressure of oxygen. The PO_2-vs-time curve that the cells experience is of great importance to the way in which they sickle, so the gas system has been designed to allow the oxygen saturation to be changed quickly and reproducibly (e.g. from arterial to venous levels). A video camera connected to an inverted microscope transmits the image to a digital frame grabber in a Macintosh II computer. We are developing pattern recognition algorithms to determine which of the cells in the field of view has sickled. The same image analysis program is being modified to control the flow and concentrations of gas passing by the cells. The new system will eliminate the tedious manual cell counting that has been used in the past, and we hope that eventually it can be used by clinical researchers to monitor patients and to help develop new therapeutic agents to reduce the severity of the disease.

A new project has been initiated to perform the mechanical design of an improved anti-scatter grid in a mammographic imaging system. Mammography plays a vital part in the early detection of breast cancer and has received a great deal of attention recently in the press—regular mammograms are now recommended for all women over the age of 40. Since more mammograms will be taken, it is extremely important to reduce the dose to the patient. The new device will significantly reduce the patient dose while maintaining satisfactory image quality. The most important new feature of the design is the presence of an array of thin metal vanes arranged in an arc about the x-ray source, between the breast and the film. The vanes absorb scattered radiation, and thus improve the quality of the image. In order for the vanes not

to image on the film, the grid must move in a precisely controlled profile during the exposure. This motion will be controlled using a stepping motor with programmable motion profiles. Sensing of the position of the grid will be accomplished using high-speed fiber-optic sensors.

This year, in collaboration with NINDS, the Section has begun a detailed study of the electric field induced during magnetic stimulation. This technique for stimulating neurons is noninvasive and painless, but the site and focality of the stimulus is not always predictable. Using computer simulations, the electric field in the arm and the brain have been calculated for various coil geometries and orientations. In addition, the interaction of the induced electric field and a nerve axon has been studied using a nonlinear cable model. Together, these simulations provide much insight into exactly where and when magnetic stimulation occurs. These models are being used to design new coils that deliver stronger, more focal stimuli. Another collaboration with NINDS involves measuring the magnetic field produced by action potentials in a peripheral nerve. These measurements, performed with a superconduction quantum interference device (SQUID) magnetometer, can be used to obtain an image of the current distribution along the nerve. After validating the model with studies on normal volunteers, this technique will be used to monitor nerve regeneration noninvasively in individuals suffering from localized nerve injury.

Work continues on the system for three-dimensional histological reconstruction based upon a remotely controlled miniature microtome, located inside a scanning electron microscope. A mechanism for removing cut sections has been designed and tested, as well as a new technique for maintaining consistent section thickness despite variable heating.

A microcomputer-based instrument for delivering precisely one cell into each well of a titre-tray is near completion. The instrument, based on a Coulter-counter technique, should significantly improve efficiency of cell cloning. All hardware has been built and tested, and the software is currently being tested.

Scientific Equipment Services

Scientific Equipment Services (SES) is continuing to provide the NIH scientific community with equipment design, fabrication, repair, and rental services. During the past few years, SES has striven to increase the number of instrumentation-related services it offers to the NIH scientific community, improve efficiency, reduce the time researchers spend in non-research activities (such as equipment procurement and equipment repair), and reduce the cost of services provided. Specific activities are:

1. **Sale of New Scientific Equipment:** Effective FY90, SES will begin to sell commonly-used laboratory instruments, such as pH meters, waterbaths, and spectrophotometers. BEIB will stock these instruments and researchers will be able to obtain them within one day, instead of going through the normal NIH procurement process. Aside from the convenience to the researcher, we anticipate dollar savings to the NIH through reductions in the number of purchase orders processed by procurement and through decreased delays in research projects.
2. **Sale of Equipment from the Scientific Equipment Rental Program (SERP) Inventory:** In response to requests from the Institutes, researchers who rent equipment from SERP for more than six months can now purchase the equipment. (In order to prevent the possibility of a rapid depletion of SERP inventory, however, sales will be limited to 25 percent of the value of equipment that the Institute rented on the last day of the prior fiscal year.) During FY 89, $1,000,000 worth of equipment was sold to researchers.
3. **Equipment Management Program for Patient Care Equipment:** SES is continuing the development of a comprehensive program for the management of patient care equipment in the Clinical Center. The program includes equipment evaluations, incoming/new equipment inspections, electrical safety testing, performance testing, and an on-line system that reports on equipment inventories and repair histories. This plan is intended to reduce maintenance and repair costs and provide the Clinical Center with up-to-date information about its equipment.
4. **Reduction in the Cost of Manufacturer's Full-Service Maintenance Contracts:** In FY 89, SES initiated a program that offers researchers an alternative to the full-service contracts sold by equipment manufacturers. In FY 89, SES began by selling alternative contracts on a number of models of Coulter Counters. In FY 90, the contracts were expanded to include a number of models of Gilford spectrophotometers and Dupont/Sorvall centrifuges. These contracts are priced about 30 percent lower than those offered by the equipment's manufacturers.
5. **Laboratory-Wide, Full-Service Contracts:** In FY 90, SES will initiate the first phase of a program that will permit researchers to have one contract for the maintenance of all of the equipment in their laboratory. During phase I, SES will sell a limited number of contracts to researchers, covering the equipment in their laboratories which we currently repair on a fee-for-service basis. We expect to expand these contracts in FY91 to cover a

wider range of instruments and to offer the program to the entire NIH scientific community.

6. **Reduce Maintenance Costs:** SES has initiated a review of the costs of in-house and contracted maintenance costs of specific types of instruments. The goal of this program is to develop a program for directing repairs to the least costly source.

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Personnel of the NIH Library (Library Branch, DRS). (Photograph taken for the first DRS Employee Recognition Day, June 1, 1989.)

Library Branch

Carolyn Brown, Chief

Fiscal Year 1989 saw growth of service and a consolidation of improvements in many areas of the Library. Staff learned to make the best of new technology available to them and to manage it with increasing skill. A move of many older journals to a storage area freed shelf space for incoming material and made reshelving tasks easier. As staff retired or transferred, a gradual move to contract for all shelving and much of photocopy took place; restructured tasks then resulted in a more smoothly functioning operation. Library outreach services broadened in scope and extended to almost every institute, following a trend of the past few years. Demand for traditional services such as photocopying and interlibrary loan continued the move upward. And a concrete design for a new reading room made an appearance.

Automation

The planned migration from an interconnected group of systems to one integrated system proceeded in stages. In the beginning of the fiscal year the new online catalog was introduced. It was an immediate success. Ease of use is its hallmark. Unlike its predecessor, it requires no printed instructions and almost no questions have been asked about its operation. Holdings and availability are displayed for every item in the collection; information is also given about material on order. The circulation system shows whether an item is charged out and when it should be returned. The journal system displays journal issues as soon as they are checked in, and also notes when they are sent to the bindery. For the first time ever, camera-ready copy for the Library's serials list was produced in-house by capturing journal records from the Library's database. The editing done for the printed version also benefitted the online catalog.

Taking advantage of a training program in word processing, staff in all sections have restructured and restored files to make them more easily usable and in some cases to effect substantial savings over storage on an external computer. The Readers Services Section has begun to employ Lotus programs for maintaining and manipulating statistics.

At the end of the year, the first CD-ROM system was acquired and was being tested by staff to determine the best means of presentation to users.

Executive Plaza Storage

Journal titles or parts of titles that were observed to be infrequently used were moved to a leased area in the Executive Plaza South building, freeing many linear feet of shelving in the NIH Library. These titles remain on a list drawn up with assistance of the Library Advisory Committee and many other scientists, consisting of journals considered essential for NIH Library holdings. They are available from the storage area on demand, with messenger service provided within a few hours, or they can be photocopied on site. In May the storage annex was opened three days a week as a part-time reading room and information center. It is staffed from 10:00 a.m. to 3:00 p.m. Monday, Wednesday and Friday. Reference librarians register cardholders, answer reference questions, act as liaison to the NIH Library collection and perform computer searches for the sizable contingent of NIH staff located in or near Executive Plaza. There is also a small collection of current journals, to be maintained for no more than two years, for reading by the local group. A survey was made to determine which titles would be of most value. Some of the NIH staff at Executive Plaza have offered to give their copies of journals to the annex when they are no longer needed. The Library is waiting to analyze usage in the annex before deciding which offers to accept.

Coin-Operated Photocopy

The review of the Library's services completed two years ago noted the heavy burden imposed by public use of the Library. At one point another study showed that half of the readers in the Library were non-NIH. Although no actual count by category of user has been made this year, there are indications that the public presence continues to increase. Use of the pay photocopy machines has grown by approximately 15 percent over 1988, which in its turn increased 12 percent over 1987. The trend has been upward by 11 to 29 percent each year since 1985. Shelving from areas that include bookshelves for materials used at the pay photocopy machines has increased a little over 7 1/2 percent from 1988 to 1989. Reasons for this continuing growth in use of coin-operated copiers are unclear. Changes in accessibility of material in the National Library of Medicine may play a part. Alteration in policy there has meant a limitation on the number of items that can be requested in one day. The ready availability of volumes on open shelves in the NIH Library is undoubtedly a convenience for the outside user.

and some who once would have used NLM now come to NIH. This is a service increase that the Library is ill equipped to accept but has no practical means to refuse.

Journal Review

In 1988 a five-year review cycle was completed that had brought under scrutiny every title on the Library's subscription list. In that five-year period approximately 750 journal subscriptions were cancelled. New publications needed by researchers were acquired in the same time span that fairly well annulled any saving of space and subscription costs resulting from the review. In 1989 second copies of certain titles were reviewed carefully and 47 of such second copies were cancelled for insufficient usage.

Subscription cost increases of medical and scientific journals over the past ten years have dismayed librarians, who see their budgets being overwhelmed by this one item. It has gradually become clear that the preponderance of the increase is concentrated in the hands of a few foreign publishers, who continue to raise prices without any apparent justification other than the belief that libraries are a captive audience. The problem goes beyond the power of librarians to repair and is centered about the publishing demands in scientific fields. Librarians are seeking allies in their attempt to restore some balance to yearly expenditures. The NIH Library will monitor carefully the usage of these very expensive specialized journals, and will hope to inform scientists of the dangers inherent in current directions in publishing.

Service Trends and Improvements

A copier-control system was installed in the self-service photocopy area. The control is a timing device that allows each user five minutes of copy time when others are waiting. This has proved to be a more satisfactory limiting mechanism than the old method of allowing 30 copies, which had to be monitored by the attendant, a never very satisfactory arrangement. The new timers have accelerated the copying process, apparently because the slower operators are forced to move faster or go back into the waiting line. Almost no complaints have been heard about the new service. Use of self-service copying has increased slightly in the past year. Use of the request service for photocopies or loan has increased approximately 60 percent.

Demand for personal tutorials and consultation has continued to grow. Project assistance in many institutes has included the development of indexes for reprint files; advice in setting up and managing small libraries; writing articles for a newsletter; downloading references from Medline into a software package that permitted numerical analysis; helping to create a database; and assisting in microcomputer training for a new class of scholars at the Howard Hughes Medical Institute. At least one Medline or Grateful Med class is given each week.

The circulation service showed a slight increase of 2 percent, just half the increase seen last year.

The number of people entering the Library increased 3 percent over FY 88. The increase last year was 4 percent.

Staff Development

The Library is fortunate to have a talented and dedicated corps of professional and support staff who try to make a continuing contribution to the NIH and to the library profession at large. This year they found time to provide cross-training seminars for each other so that all members could become acquainted with work in other areas of the Library.

Interest in this type of program had been expressed by staff members for several years. In the summer of 1989 a cross-training committee composed of staff sent a questionnaire to determine what classes were wanted. As a result, a series of overview sessions two to three hours in length described the work performed in each area. The session most in demand was a two-hour explanation of the operations of the Library's computer. The cross-training committee conducted an evaluation that showed that nearly all of the students felt the training was personally useful. In the majority of cases, staff chose training that would enrich their skills in the current job. Those who want to pursue training in greater depth will be given the opportunity to do so.

New Reading Room

Library staff participated this year in a requirements analysis and development of design for a new reading room. It involves enclosure and extension of the present Library patio to provide an upper floor for the medical intensive care unit and a ground-level expansion of the existing reading room to create a much larger public area for Library users. A larger reading room was recommended in the study of the Library completed in 1987 by King Research, and has long been desired by staff and users. Construction may begin in late 1990 or early 1991.

Library Advisory Committee

The Library has always had an advisory committee consisting of one member from each of the BID's except the smallest. This committee advises and assists, gathers opinions of colleagues, con-

veys complaints and suggestions, writes letters, recommends positions and presents them to authorities, acts as a sounding board, makes pleas for money or space, defends the Library, and in general is collectively and individually a good and valued friend. The committee plays a large role in keeping the Library operating effectively.

Services of the NIH Library

The NIH Library offers a full array of services to assist scientific investigators in their work. They include:

- **Computer Bibliographic Services** - Technical specialists perform computerized literature searches and compile bibliographies upon request. The staff is experienced in retrieving citations and abstracts from some 155 scientific databases. (Request from Reference and Bibliographic Services.)
- **Current Awareness Service** - The Library's Selective Dissemination of Information (SDI) program provides users with regular computer updates on new literature in the biological and medical sciences. (Request from Reference and Bibliographic Services.)
- **Reference Services** - Reference librarians not only answer reference questions on site or by telephone (496-2184) but also advise users of other library services that may meet their needs.
- **Photocopying** - Copy machines are available to users in a self-service area. (Photocopy Service, lower level.) The library also will locate and copy articles upon request. (Request form at Circulation Desk.)
- **Microfilm and Microfiche** - Many journals are also kept in microform. Most are backfiles of important titles, acquired in order to save space. Reader-printers are reached through the Photocopy Service.
- **Circulation** - Books other than reference works and noncirculating reserve items can be checked out. Second copies of some of the most popular journals are also available for circulation.
- **Interlibrary Loans** - Research publications and photocopies of journal articles not in the collection can be obtained from other libraries.
- **Advisory Service to NIH Branches and Laboratories** - Staff of the Library will advise on organization and maintenance of office collections and on development of computerized search capabilities. (Request from Chief, Reference and Bibliographic Service Section.)
- **Translations** - Foreign language scientific materials are translated upon request from NIH staff. All translations are made available to other users.
- **Stacks Service** - Library staff will search for any volume a user cannot find on the shelves. (Request form at Circulation Desk.)
- **Publications** - "Recent Additions to the NIH Library" is available monthly in printed form. "Current and Noncurrent Journals: NIH Library" is published biannually. Copies are available from the Circulation Desk.
- **Library Tours** - A tour providing an overview of NIH Library services and policies is available every Wednesday at 2 p.m., beginning from the Reference Assistance Desk.
- **Carrels** - Private study carrels are available on a limited, first-come basis. (Circulation Unit.)
- **Instruction** - Instruction on the use of the NIH Library is offered periodically. "MEDLINE for the Health Professional" is taught monthly. (Further information is available from Reference and Bibliographic Services.) Staff will also give laboratory tutorials in MEDLINE.
- **"NIH Library . . . in Brief"** - This eight-page Library guide is available upon request at the Circulation Desk.
- **Information Sheets** - One-page information sheets on specific services are available at the Circulation Desk.

Personnel of the Medical Arts and Photography Branch, DRS. (Photograph taken for the first DRS Employee Recognition Day, June 1, 1989.)

Medical Arts and Photography Branch

Ronald B. Winterrowd, Chief

The Medical Arts and Photography Branch (MAPB) is a central service organization which provides a wide variety of visual communication services to the NIH community. MAPB's products and services visually document scientific data, research programs, events and accomplishments for use in publications, exhibits and presentations to the worldwide scientific community and the general public.

The Branch is staffed by professional artists, photographers, and other specialists who are experts in converting diverse data into effective visual presentations. Their talents and skills are challenged daily in meeting the needs of scientists for graphic presentation, medical arts, photography (including photomacrography and photomicrography) and video production. Services include design and production of publications, preparation of slides, vugraphs, and other projected visual aids, exhibit design, statistical drafting, display charts, posters, medical illustrations, video recording, and support for special events.

The Branch's long-standing philosophy is to provide high quality professional services competitive in cost with commercially obtainable services. The staff works closely with private sector vendors of design, graphics, video, and photography services to ensure that MAPB's quality standards are maintained.

During FY 89, MAPB continued to meet the NIH community's constant and heavy demand for services. In-house services were again supplemented by the coordination of job requests with a wide variety of small businesses in the Washington metropolitan area. Competition among qualified vendors and daily bid sessions continued to ensure cost effectiveness while maintaining quality.

Major projects continued to reflect the emphasis on public education and prevention of health problems. MAPB is constantly upgrading and enhancing present equipment to meet the ever changing demands for services. Additional computer equipment was acquired and software packages upgraded in support of computer graphic services. With the purchase of MACII terminals, and the addition of new personnel, MAPB is now able to offer computer-enhanced publication designs to clients. The purchase of new photomicrography equipment has enabled the Branch to expand its services in this much-used specialty.

The findings of the evaluability study, performed last year, indicated the need for further review. This year the Branch will undergo a productivity review that will involve developing information describing program objectives, performance indicators, and major problems and issues. Also included in the study will be a detailed analysis of cost, personnel, facilities, operations, organization procedures, and user satisfaction. The study is to be completed in FY 90.

During the year, NIH implemented the Service and Supply Fund Activity System (SSFAS) so that expenditures for Service & Supply Fund Activities can be more timely tracked for budgetary purposes through the Administrative Data Base (ADB). Through hard work, planning, and coordination with the Division of Computer Research and Technology (DCRT), the Photography Section is now fully operational on SSFAS. It is anticipated that the other MAPB sections will be operating through the ADB before the end of FY 90. The Branch continues to offer its users an opportunity for information exchange through either the MAPB Advisory Committee or a staff team which is available to visit laboratories and offices to explain MAPB services, offer cost-saving suggestions, and invite recommendations on how MAPB services can be improved.

Photography Section

The Photography Section provides central photographic services to the NIH community including general (information) photography, patient and surgical photography, photomicrography and photomacrography, and photographic laboratory

processing. In order to accommodate the constant high volume of requests for laboratory services, the section continues to utilize a diverse range of photographic facilities in the Washington area.

The Section remains involved in the testing of digitally enhanced electronic imaging for photomicrography. During this effort, positive response has been received from the research community because of the equipment's ability to capture extremely low light level fluorescence, digitize, and improve image clarity at both low and high power magnification.

In addition, a new patient photography studio will be occupied in FY 90 on the first floor of the ACRF. This location will ease both inpatient and outpatient access and provide a safer, more attractive, and functional environment, with nearby medical personnel in case of an emergency situation. The updated studio facility will also improve the quality and consistency of patient photography.

The Section is currently utilizing the SSFAS for all photographic work ordered. This billing mechanism allows BIDs and requestors of photographic services to maintain a continuous review of expenditures.

Design Section

The Design Section employs graphic designers and illustrators who provide various design services to the NIH community. Many of these skilled and experienced designers have won awards in local, national, and international competitions. The Section provides publication design for public information, scientific presentations, poster design, editorial and technical illustrations, and other services that may be required to support the research effort of the NIH. The Section also designs and produces support materials for conferences held at NIH.

FY 89 saw more computer-assisted design. Three more work-stations were acquired to handle the workload associated with publication design and pre-press needs of our NIH clients.

Graphics Section

The Graphics Section consists of two units—Graphics and Special Events. These units are composed of professionally trained, highly skilled and experienced illustrators, visual information specialists, exhibit specialists, and TV production specialists.

The Graphics Unit provides illustrations, charts, graphs, tables, slides, computer generated graphics, and other materials for scientific publications and presentations at meetings. The requests for computer-generated productions continue to rise, and the unit is continually upgrading software to accommodate the various needs of requestors that use this service.

The Special Events Unit provides support for unusual or one-time events including scientific poster sessions; exhibit design and fabrication; sign system design and production; medical and scientific videotaping, editing, and duplicating; Medicine for the Layman lectures (slide shows); and other special requests. The addition of an in-house script writer for video will increase the capabilities of video. The in-house editing suites will be completed shortly and will enable in-house editing.

Medical Illustration Section

The Medical Illustration Section produced a wide variety of black-and-white and color medical illustrations and diagrams of surgical gross pathological, ophthalmological, biological, and dental subjects. During FY89 the Section continued to participate in public information projects, with medical illustrations used in poster designs, public information brochures, exhibits, and newsletters. Work continues on a long-term project for NCI involving illustrations for the "Atlas on Oncologic Surgical Techniques."

Outlook for FY 90

MAPB will continue to provide the NIH community with the highest quality service at the lowest possible cost by competing prices among MAPB vendors, increasing in-house productivity, and informing clients of methods which may reduce job costs.

MAPB's productivity study will be awarded and implemented.

Personnel of the Veterinary Resources Branch, DRS. Top picture: Employees of VRB Bethesda operations. Bottom picture: VRB employees of the NIH Animal Center, Poolesville. (Photographs taken for the first DRS Employee Recognition Day, June 1, 1989.)

Veterinary Resources Branch

Stephen Potkay, V.M.D., Chief

The Veterinary Resources Branch (VRB) provides professional and technical support service for NIH intramural programs. It is responsible for:

- Housing research primates, cats, dogs, rodents, rabbits, poultry, and livestock
- Coordinating management and providing technical support for research projects conducted with animals housed in VRB facilities
- Procuring, quarantining, conditioning, and issuing animals from outside sources
- Diagnosing and controlling animal diseases
- Producing defined research animals
- Managing central animal surgery and radiology facilities
- Maintaining an international laboratory animal genetic resource
- Providing consultative services on animal health, care, husbandry, genetics, and nutrition

During FY89 the Branch continued to be active in meeting all of these responsibilities.

A major, in-depth, Branch-wide management analysis was begun using the services of a contractor and directed towards increasing the organization's responsiveness to the current and foreseeable needs of NIH intramural research programs. The initial product was a comprehensive mission statement which reflected this revised role. Thereafter, the focus shifted to organizational and programmatic aspects, with input being solicited from all Branch employees, institutional veterinarians, and many scientists who utilize VRB products and services. Recommendations to streamline, modernize, and otherwise enhance the VRB organization were being prepared, based on the information received, as the fiscal year drew to a close. The contractor also collected, evaluated, and compiled data which were used to establish needed equipment inventories, assess the physical condition of facilities, and standardize the operating procedures used throughout the Branch. This information also proved valuable in preparing for the triennial site visit by representatives of the American Association for Accreditation of Laboratory Animal Care (AAALAC).

Considerable attention was given to developing short- and long-term plans to renovate existing facilities and provide new facilities throughout the Branch to house and utilize research animals. Work was initiated on a number of programs of requirements (POR's) directed towards improving the housing available for swine and other livestock, dogs and nonhuman primates, while the POR was completed for a large building (Building 14C) destined to house research rodents and rabbits owned by other NIH Institutes, Centers, and Divisions (ICDs). Completion of renovations permitted the placement of foundation and nucleus colonies of guinea pigs, rabbits, and hamsters into modernized facilities. Unfortunately, delays in renovating the new specific-pathogen-free (SPF) barrier extended into their second year, thus preventing the relocation of the nucleus mouse and rat colonies. Significant progress was made, however, towards establishing a new central facility for research rodents and rabbits. Renovations to Building 10A reached the 90 percent completion mark, virtually all of the required equipment was ordered, key staff members were recruited, specifications for a contract staff were prepared and submitted, and intraagency agreements were negotiated with the twelve user ICDs. In the Clinical Center (CC), the Branch agreed to assume responsibility for cagewashing operations in addition to coordinating animal-related activities in the ACRF tower and continuing to provide veterinary support for CC animal research programs.

Other activities included assisting the Office of Animal Care and Use (OACU) in establishing a pilot study to determine the utility of a commercial computer program in helping to manage animal facilities throughout the NIH. Similarly, VRB made its facilities available for another pilot study of a commercial system designed to monitor environmental parameters in animal facilities. Efforts were extended to assist in the conduct of site visits for Congressional and Departmental staff interested in laboratory animal care and use. Extended instruction in this field was also offered to trainees from Spain, Brazil, and China, while more specialized, intensive short-term training was provided for a number of U. S. students.

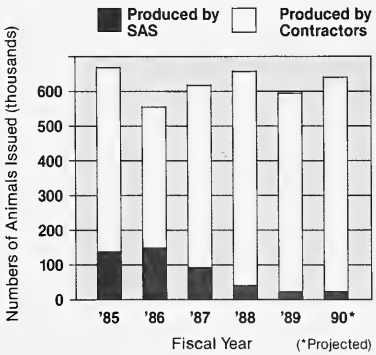
Small Animal Section

The Small Animal Section provides rodents and rabbits to the NIH intramural program through its in-house and contract production programs. It also manages the NIH Animal Genetic Resource (NIHAGR), a research animal holding activity, and programs in animal nutrition, model development, health, and embryo cryopreservation.

Ordering and Contracting Unit. This activity provided 595,554 rodents and rabbits, 98 percent of them from contract sources, for NIH intramural research (Figure 1). Contracts included nine of the indefinite delivery type with commercial breeders and one research contract with the Division of Cancer Treatment, National Cancer Institute (NCI). Animals from all sources were periodically monitored for pathogenic organisms. Efforts were begun to handle the receipt and confirmation of requests for animals through the use of fax instead of telephone in order to reduce the likelihood of error and to speed the process. Trial billings are being made using the VRB Animal Data System. This system should improve efficiency.

NIH Animal Genetic Resource. This activity continued to evolve in its role of developing and maintaining models of small research animals utilized in biomedical research. The NIHAGR made major contributions to a variety of research areas during the past year. First, it is now recognized as a major resource of immunocompromised rodents, primarily as the result of work with immunocompromised mice where it was found that human myeloid tissue will grow when transplanted and produce human cells. This represented a major breakthrough for a variety of research areas including AIDS, cancer, and resistance and susceptibility to bacterial and viral infections. The primary advantage of this model is that it can act as a multi-cellular tissue culture system. The second contribution dealt with developing a rat model which appears to be valuable for the study of cause and effect relationships involved in rheumatoid arthritis. The third major achievement was the further characterization of a rat model for insulin-independent diabetes mellitus. Other models for different areas of biomedical research are under development and should become available to the research community over the next few years.

Figure 1
Numbers of Rodents and Rabbits Issued by The Small Animal Section (SAS)



Production Unit. This Unit provided the management and facilities required to support the NIHAGR and maintained small production colonies to meet special NIH needs. Partial renovation of Building 14F allowed the relocation of all the conventional rabbit, guinea pig, hamster, and cotton rat nucleus and foundation colonies from Building 14C. Completion of the Building 14F barrier renovation is anticipated in FY90, when transfer of the mouse and rat colonies by cesarean derivation or embryo transfer from Building 14G will commence.

Research Support Unit. This Unit held rodents and rabbits and provided technical and professional support for 105 investigators from twelve institutes, the CC, and the Food and Drug Administration (FDA). Animal holding increased by eight percent compared to FY88 not including that provided under four intraagency agreements. The gnotobiotics activity processed four rat and eleven mouse strains for eventual introduction into the new barrier facility and provided germ-free rats to contractors. The program of requirements for renovating Building 14C to provide additional research rodent and rabbit space was completed. Design and construction await the availability of funds.

Nutrition. There were no reports of nutritional problems associated with NIH animal diets during the year. The seepage of fats from diets manufactured by extrusion was resolved when the feed contractors used more appropriate bags.

Numerous modifications were made for ICD scientists in the formulations of open formula diets and the AIN-76 purified diet to accommodate specific research requirements. Diets used at the Nonhuman Primate Conservation and Reproduction Program in Iquitos, Peru, were also modified to permit utilization of feed ingredients common in that region.

Research activities were largely collaborative, involving ICD scientists and investigators from other institutions. One such project involved participation in a National Institute on Aging (NIA) study of dietary restriction in primates that will span 15 to 20 years. Similar involvement is ongoing with scientists from the Jackson Laboratory and Battelle-Pacific Northwest Laboratory. Other collaborative efforts are concerned with the effects of dietary macronutrient concentrations on blood pressure in studies conducted by Georgetown University, the development of diets for the National Institute of Environmental Health Sciences (NIEHS) that are suitable for long-term

toxicology studies, and the formulation of diets for the National Air and Space Administration (NASA) to be used in zero gravity environments.

Animal Health. Suspension of breeding eliminated pneumonia virus of mice (PVM) from the guinea pig colonies as they were moved to Building 14F. These colonies were also treated to eliminate *Chirodiscoides caviae* infestations. The hamsters are currently being treated to eliminate *Demodex* sp. and *Syphacia* sp. Eradication of Theiler's mouse encephalomyelitis virus (TMEV/GD VII) and PVM will be accomplished when the mouse colonies are rederived into the new barrier facility. These agents are present in the present barrier, but are not associated with clinical signs.

Outbreaks of sialodacryoadenitis (SDAV) and Killam's rat virus (KRV) in the Research Support Unit were quickly eradicated. Titers tc mouse hepatitis virus (MHV), PVM, and GD VII, however, continued to be detected in the mice housed there.

Embryo Cryopreservation. The embryo cryopreservation program is involved in studying the development and cryobiology of small laboratory animal embryos and gametes. The long-term goals are to enhance colony reproductive efficiency and improve cryostorage of valuable genetic material within the NIHAGR.

Since 1984, approximately 38,000 embryos have been permanently banked; this number represents a minimum of 1000 embryos obtained from each of 35 genotypes maintained in the NIHAGR. As in the past, emphasis was placed on using embryo transfer procedures in mice to routinely produce live pups. In addition, work involving the transfer of thawed embryos continued.

A new project was initiated to study the reproductive biology of rats maintained in the NIHAGR. It is anticipated that techniques used in mice will require modification for their use in rats, and work is proceeding to develop procedures applicable to embryo production, collection, culture and cryopreservation in this species. In addition, work continued on rabbit embryo cryopreservation.

The major thrust of the laboratory in FY90 will be placed on rederiving mouse genotypes from Building 14G to newly renovated barrier facilities in Building 14F. Other projected work includes evaluating sperm morphology relative to certain mouse and rat genotypes and the cryopreservation of mouse sperm.

Veterinary Medicine and Surgery Section

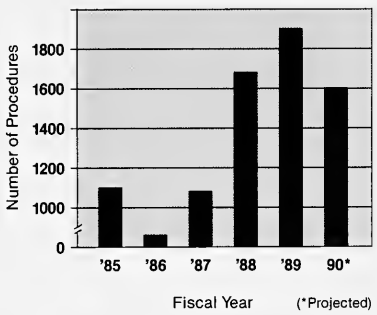
The Veterinary Medicine and Surgery Section maintains centralized facilities for large research animal holding and experimental surgery. It also provides routine care and comprehensive veterinary support for animals housed in the facilities. Section personnel provide consultations and direct assistance for NIH investigators, assist with the development of animal models for intramural research, and support active projects utilizing animals.

Surgery Unit. The Surgery Unit offers expertise and an optimal environment for aseptic surgical research. It handled 1900 cases this year compared to 1690 in 1988 and 1087 cases in 1987 (Figure 2). This sharp increase over the last 2 years reflects the support given to the NCI for kidney transplantation, bone marrow transplantation, intraoperative radiation therapy work, heart transplantation, and laser surgical evaluations while the NCI surgical facility was being remodeled. Indications are that much of this work will remain in the Surgery Unit after renovations to the NCI facility are completed; this will necessitate additional personnel in order to provide adequate technical support.

Substantial support was also provided to the National Heart, Lung, and Blood Institute (NHLBI) to study succinylacetone and various other immunosuppressive drugs following heart transplantation to see which are beneficial for retarding or preventing rejection. In addition, studies to evaluate which concentrations of fibroblastic growth factors will increase vascular development and collateral circulation in the heart following ischemic injury have escalated. Surgery Unit support was provided to more than a dozen other research projects from a variety of institutes.

Primate Research Unit. This Unit housed 730-760 primates representing nine species, which were used in research projects for eight institutes, OACU, VRB, and the CC. When renovations to Building 14D are complete, the total inventory will rise to about 780. The primate recycle program continued to operate at variable low level.

Figure 2
Surgical Procedures Performed



Nine intraagency agreements were in effect for at least part of the year. When NCI relocates its programs to newly renovated space, two rooms will become available for other research and one will become a treatment and recordkeeping area.

The Unit continued to work towards maintaining standards required by AAALAC and the NIH *Guide for the Care and Use of Laboratory Animals*. Virtually all of the floor renovations were completed and the majority of the ceilings were repaired or replaced. The baboon rooms were renovated and all the Unit's animals were housed in appropriately sized cages. The east cagewasher will be rebuilt in FY90.

A number of boxes were made for use in transferring animals from cage to cage. The use of these boxes will greatly reduce the need to use chemical restraint when moving animals. After further definition of their design, more boxes will be ordered.

Several clinical cases of simian acquired immune deficiency syndrome (SAIDS) were diagnosed. Approximately one-third of the animal rooms in the Unit now house only animals which have tested negative for simian retrovirus (SRV) and simian immunodeficiency virus (SIV).

Comparative Medicine Unit. This Unit provided centralized animal holding, veterinary care and consultation, and technical support to projects from ten different institutes at NIH. The projects involved the use of dogs, cats, sheep, miniature swine, ducks, and chickens. Numerous short- and long-term projects of varying size were supported throughout the year.

The NCI continued to be a major user of the Unit's services. Miniature swine were used as models for bone marrow and other organ transplantation studies, and a significant number of the pigs used in these projects required extensive postoperative intensive care. Completion of NCI's new facilities was delayed but is now expected early in FY90. This will probably reduce swine holding by about 25 percent. A second major NCI project involved the use of dogs to investigate the long-term effect of radiation therapy on vascular grafts and other tissues. The CC, studying the cardiovascular effects of septic shock using beagles as a model, remained a significant user of the Unit's animal holding and procedure space. This project is of nationally recognized importance in the study of the pathogenesis and treatment of septic shock. The Surgery Branch, NHLBI, continued to use sheep as surgical models for cardiovascular disease studies. The number required is projected to nearly double from the current total of about 200 per year. Foxhounds continued to be used by the NHLBI to study myocardial angiogenesis. The ongoing National Institute of Allergy and Infectious Diseases (NIAID) study to investigate the feline t-lymphotropic lentivirus as a model for HIV infection of man also achieved a level of nationally recognized importance.

The management emphasis in Building 28 was on equipment purchases and improved medical recordkeeping. All of the dog cages in one room will be replaced, and additional transport cages were ordered. The new cages will be sanitized in the Building 14A cagewash. A fax was installed to facilitate the transfer of animal records between the Unit and the Animal Center Section. Numerous recordkeeping forms were designed and printed; they are the basis of a temporary paper recordkeeping system that will remain in place until a computerized system is implemented.

Animal Center Section

The Animal Center Section supplies, maintains, and develops large laboratory animals for use as models of human disease and provides related services and products for NIH investigators. The animals involved are mainly primates, farm animals, dogs and cats. Veterinary support and services are provided to intramural investigators who utilize these animals at the Animal Center or who require animal by-products such as blood and serums.

Carnivore Unit. Purpose-bred beagles and coonhound-type dogs were obtained from a contractor for use in NIH research programs. The socialization program for the latter is being strengthened to ensure that dogs of appropriate quality are issued to investigators.

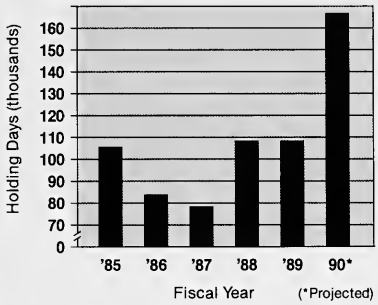
An intraagency agreement was renewed to support the National Eye Institute (NEI) diabetes research project which utilizes beagles; it is anticipated that these studies may continue for another five years. Research involving the ability of drugs to alleviate anxiety in naturally nervous pointers was resumed by the National Institute of Mental Health (NIMH).

A number of projects were continued in collaboration with the Uniformed Services University of the Health Sciences (USUHS) and the National Zoological Park (NZP). These included studies of factors affecting *in vivo* and *in vitro* fertilization and embryo development in domestic and wild species of cats. This work has bearing on the propagation of difficult-to-breed and threatened species.

Figure 3 shows the past and projected activity levels of the dog and cat long-term holding program at the Animal Center.

Ungulate Unit. The use of lambs by the NHLBI was far greater than predicted, and difficulties were encountered in obtaining high quality animals. The Unit produced 105 lambs which were issued at times when no others were available. The need

Figure 3
Research Holding Provided for Dogs and Cats



for lambs in FY90 is estimated to be greater, and the use of normal sheep blood is also expected to increase.

The NCI reduced its herd of miniature pigs from 360 to 300 head, but the size of the breeding herd was unaltered. Over 390 live pigs were born—the most in a single year since the herd was established in 1972. More pigs were used in surgery than in previous years.

Artificial insemination and embryo transfer efforts will continue in collaboration with the NZP to establish a flock of sheep homozygous for hyperbilirubinemia.

Primate Unit. Principal activities continued to be long-term (more than 1 year) and short-term holding of primates on a variety of protocols. The unit operated for the second year with a zero pre-order inventory; orders were placed only after projects were identified and when space was available. A contract was awarded late in the fiscal year for rhesus (*Macaca mulatta*) monkeys of Chinese origin. Cynomologous (*M. fascicularis*) monkeys were procured competitively as needed. The availability of New World primates through the Pan American Health Organization is expected to continue.

Approximately 25 percent of the Old World monkeys in the Unit were tested for simian retroviruses (SIV and SRVs; negative animals were housed separate from infected monkeys.

Quarantine policies and procedures applicable to primates destined for research at the NIH were strengthened and promulgated to users. The purpose was to avert the introduction of diagnosable infectious diseases into research colonies and to improve the health status of monkeys issued.

Research projects of several institutes were supported by the Unit. One of these involved studies to determine the effects of dietary restriction on longevity of rhesus and squirrel (*Saimiri* sp) monkeys conducted by the NIA. Because of the long-term nature of this project, psychological enrichment was an important concern which is being addressed by modifying housing to enhance visual and direct physical contact and to promote activity. Collaborative efforts involving the National Institute of Mental Health (NIMH) and National Institute of Child Health and Human Development (NICHD) focused on photoperiodicity relative to reproduction. Relationships between light cycles and molting as well as testicular size have been noted. Studies are under way to evaluate the role of the hypothalmus in these processes.

Studies to determine the effects of thromboxane synthetase inhibitor on gravid rhesus monkeys were undertaken in collaboration with the Virginia Polytechnical Institute. The goal is to define the usefulness of the rhesus monkey as a model for preeclampsia.

In addition to efforts directed towards providing psychological enrichment mentioned previously, other measures related to environmental enrichment included installation of mirrors on the walls of animal rooms, award of a contract to produce a large "family type" cage unit, and work to winterize outdoor corncribs to permit their use throughout the year.

Comparative Pathology Section

The Comparative Pathology Section characterizes and improves the health status of laboratory animals and studies the naturally occurring diseases of those produced, quarantined, or utilized in biomedical research at the National Institutes of Health. It also monitors the genetic quality of NIH animals, which are used worldwide in research and testing. Laboratory animal disease diagnosis is performed by a staff of pathologists and microbiologists to aid in the control and elimination of disease in a wide variety of animals maintained in conventional, germfree, and barrier-sustained colonies. Research is conducted on the pathogenesis of naturally-occurring diseases of laboratory animals to facilitate both diagnosis and control of such diseases. Monitoring the genetic integrity of inbred mice is accomplished by testing for groups (profiles) of characteristics (markers) thatntify the genetic constitution of each strain. A variety of consultative services and instruction is provided to ICD investigators and veterinarians related to the diagnosis and control of diseases in NIH research laboratories. Importation and quarantine services are provided to permit the introduction of rodents and rodent products from non-approved sources into NIH while minimizing the risk of introducing ectromelia,

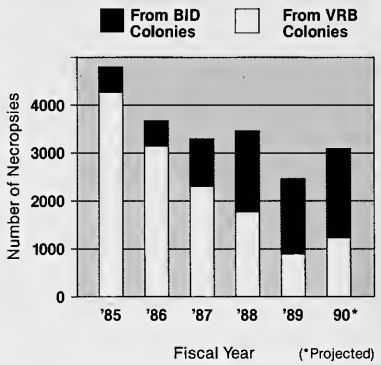
lymphocytic choriomeningitis, and Hantaan viruses. The Section also collected information to establish a comprehensive animal health surveillance and diagnostic service to meet the needs of the NIH.

Pathology Unit. The numbers of necropsies of VRB-owned animals presented by VRB declined, while the upward trend in the numbers of necropsies performed for ICD veterinarians and investigators continued (Figure 4). It is projected that these numbers may increase with the opening of new animal research holding facilities and the implementation of the animal health surveillance program during FY90. The Unit contributed considerable assistance to investigators and clinical veterinarians in diagnosing animal diseases and identifying causative factors. Substantial time was also devoted to distinguishing naturally occurring from experimentally induced diseases.

Diseases observed were attributed to a variety of conditions. Significant findings from nonhuman primate necropsy cases included tuberculosis (*Mycobacterium tuberculosis*); bacterial pneumonias due to *Streptococcus pneumoniae, Bordetella bronchiseptica, Escherichia coli, Klebsiella pneumoniae, Corynebacterium pseudotuberculosis,* and *C. ulcerans*; colitides due to *Shigella* sp. and *Campylobacter* sp.; infectious simian retrovirus (SRV); intussusceptions; lymphoma; aortic aneurysm; endometriosis; and acute gastric dilatation. In other species, significant conditions included: acute mouse hepatitis virus infections in SCID and nude mice; Sendai virus, rotavirus, *Mycoplasma pulmonis*, and CAR bacillus infection in immunocompetent mice; sialodacryoadenitis virus, *M. pulmonis*, CAR bacillus, and *Pasteurella pneumotropica* infections in rats; pneumonia in guinea pigs and rabbits due to *B. bronchiseptica*; colibacillosis in rabbits; infectious peritonitis, pyometra, and pneumonia due to *Pasteurella multocida* in cats; pneumonia in pigs due to *P. multocida* and *Mycoplasma* sp.; pneumonia in sheep due to a combination of paramyxovirus, *P. multocida* and *Mycoplasma* sp.; and caseous lymphadenitis in goats due to *C. pseudotuberculosis*.

Microbiology Unit. The total number of samples received by the Unit increased significantly, and it is anticipated that the Unit's workload will increase dramatically when NIH-wide microbiologic monitoring of animals and the environment is implemented. The serology laboratory received and processed 1,960 serum samples, almost two-thirds of which were from ICD sources, for testing. A total of 17,478 tests were performed on these samples. Approximately 60 percent of them were performed in-house, the balance being performed by a contractor. A full range of serologic tests was available in the Unit for important murine viruses and selected mycoplasmas and bacteria. This year, the contractor tested most

Figure 4
Necropsies Performed



mouse sera for EDIM. Of 862 mycoplasma cultures performed, most were negative. However, *M. pulmonis* was occasionally cultured from rats and mice housed in conventional ICD animal rooms, and *Mycoplasma* sp. was obtained from pigs and sheep with bronchopneumonia.

The bacteriology laboratory received 2635 samples which represented an increase of 27 percent over last year. Most of this increase could be attributed to more clinical specimens from the Institutes. There has been a significant rise in the number of samples from nonhuman primates and large animals such as sheep and pigs. Workloads have also increased because more tests and sophisticated procedures have been employed to improve the quality of the results. For example, monkey fecal samples were routinely cultured for shigella, salmonella, campylobacter (using two methods), and tested for vero-toxigenic *Escherichia coli*.

Approximately 3,100 procedures were performed on the 1,844 parasitology samples received. These involved routine observations for ectoparasites and examinations for endoparasites using endotape, fecal flotation, direct smear, and intestinal scraping.

Genetics Unit. Approximately 3,000 animals were received from the NIHAGR—a small increase over FY88. It is anticipated that the Unit will continue to receive between 3,000 and 3,200 animals per year for the foreseeable future.

The Genetics Unit performed more assays in FY89 than during any previous year since its inception. Similarly, it received animals from a greater number of lines (275) than during any

earlier period. Of particular interest is the 37 percent increase in the number of rats received during the year, which reflects the changing composition of the NIHAGR. This coincided with an increase in the Unit's ability to discriminate between inbred strains of rats. Work continues on the development of profiles for congenic and recombinant inbred strains of rodents.

No genetic contaminations were reported or detected in any of the strains maintained by the NIHAGR. As usual, the Unit responded to a number of requests from investigators both for information on genetic profiles and/or testing of animals obtained from colonies established with breeding pairs from the NIHAGR. It is anticipated that the number of such requests will remain constant at approximately 25 per year.

Importation and Quarantine. Fifty-two permits were issued for the introduction of rodents and rodent products. This was a 160 percent increase over FY88 and reflects the trend of using transgenic and mutant mice that are not available from contract sources.

Research Activities. General research activities were concerned with studies of the pathogenesis of diseases occurring in the animal colonies, the control of such diseases, and the development of improved methods for monitoring infectious agents and genetic purity. Research conducted in FY89 included the development of genetic profiles for inbred laboratory rodents. Additionally, a variety of collaborative studies were also carried out with ICD investigators.

Forecast

A major activity of the Branch in FY90 will be to complete the management analysis and implement its recommendations. It is anticipated that organizational, programmatic, and staffing aspects will be completed early in the year, to be followed by in-depth considerations of information, communication, and training needs as well as those related to budget, procurement, and internal policies and procedures. Activities regarding facility improvements are expected to result in clearly defined long-term plans and the initiation of several renovation projects. The Branch will continue serving as the principal player in developing plans for the construction of the animal care and use areas of the new Child Health and Neurosciences Building (Building 49), and the central rodent and rabbit facility (Building 10A) will become operational. Finally, it is expected that an NIH-wide animal health surveillance and diagnostic service will be set in place and that the issue of quarantine and isolation for rodents and rabbits will be addressed.

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